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BIOPHARMACEUTICAL STUDIES OF LIPID-CONTAINING ORAL DOSAGE FORMS: RELATIONSHIP BETWEEN DRUG ABSORPTION RATE AND DIGESTIBILITY OF VEHICLES

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SUMMARY

The gastrointestinal absorption characteristics of a drug in a lipid-containing oral dosage form were studied in rats in relation to digestibility of lipids. 1-Cyclopropyl-4-phenyl-6-chlor-2(1H)-quinazolinone (SL-512) was selected as a model of a lipid soluble drug with very low water solubility. Medium chain triglyceride (MCT) was employed as a model of a well digestible lipid and N-α-methylbenzyllinoleamide (MBLA) as model of a poorly digestible lipid.

The in vitro release experiment of SL-512 from lipid vehicle to the water phase showed a strong affinity of SL-512 to vehicle lipids. In the oral administration study of lipid preparations to rats, the serum level of SL-512 was found to be much higher from an MCT preparation than from an MBLA preparation. In the in situ recirculation experiment SL-512 was not absorbed from lipid vehicles, although it was easily absorbed from the aqueous solution. These facts suggest that digestion of the lipid was a major premise for absorption of SL-512.

In the intraduodenal administration study the serum levels of SL-512 from MCT and corn oil preparations were depressed by ligation of the bile duct. It was therefore suggested that the decrease of the amount of the lipid by digestion in the gut was important for the absorption of SL-512 in lipids.

INTRODUCTION

It was shown in our previous report (Yamahira et al., 1978) that the absorption rate of 1-cyclopropyl-4-phenyl-6-chlor-2(1H)-quinazolinone (SL-512) given in a lipid-containing oral dosage form depended mainly on the gastric emptying rate of the preparation. However, in some cases, such as in a N-α-methylbenzyllinoleamide (MBLA) preparation the contribution of digestibility of the lipid was suggested.

Bloedow and Hayton (1976) studied the effect of lipid vehicles on the bioavailability of drugs such as griseofulvin and suggested that polar digestible lipids increased the

bioavailability of lipophilic, poorly water soluble drugs without increasing their rate of absorption. However, as pointed out in our previous report, the dose administered in their experiments was so large that the reported significance of lipid digestion could be quite different from that observed in our experiments.

If the affinity of a drug to the vehicle lipid is extremely large, it can be assumed that the drug moves apparently together with the vehicle in the gastrointestinal tract, and in such a case the digestibility of the lipid would be as important as the gastric emptying rate of the same. Under such a condition, it can be expected that the absorption rate of the drug would be controlled by selecting vehicle lipids, i.e. by utilizing the digestibility of lipids the drug absorption rate can be accelerated or delayed.

In this paper, the effect of digestibility of lipids on the absorption rate of the drug administered in lipid-containing oral dosage forms was examined using medium chain triglyceride (MCT) and MBLA as typical models for well and poorly digestible lipids, respectively.

MATERIALS AND METHODS

Materials

Commercially available soybean lecithin (Ajinomoto, Japan) was used as supplied. All other materials used were identical to those employed in our previous paper (Yamahira et al., 1978).

In vitro characteristics of SL-512

The apparent partition coefficient of SL-512 was obtained by measuring the drug concentration in 30 ml of the aqueous phase on which 2 ml of the lipid solution containing the drug was placed. This was left standing for 1 week at 37°C to reach equilibrium. For the aqueous phase phosphate buffer of pH 6.0 was used.

The transfer rate of SL-512 between the lipid phase and the water phase was determined by Kakemi's method (Kakemi et al., 1972) with slight modifications. Thirty ml of buffer solution was added to a glass beaker maintained at 37°C on which 20 ml of lipid was carefully placed. The initial drug concentration in the lipid phase was 10 μM. The buffer solution was identical to that used in experiments for determining the partition coefficient. Stirring was done by means of two glass paddle wheels at the speed of 100 ± 3 rpm. Samples of 0.2 ml were drawn from the aqueous layer through a glass tubing at 30, 90 and 180 min. The transfer rate of SL-512 from the water phase to the lipid phase was calculated by multiplying the partition coefficient by the transfer rate of SL-512 from the lipid phase to the water phase.

Oral administration experiment

Male Wistar rats weighing 180–220 g were fasted for 20 h but with free access to water. Lipid preparations of SL-512 were then administered orally: 1.0% w/v MCT and MBLA solutions. The dose of SL-512 was 2 mg/kg. At the designated time after administering these preparations, blood sample was drawn from the plexus veineux ophthalmique and the concentration of SL-512 was determined as reported previously (Yamahira et al., 1978).

Intraduodenal administration experiment

Studies were made as in the oral administration experiment except under anesthesia with 40 mg/kg of sodium pentobarbital and with a dose level of SL-512 of 0.5 mg/kg. After abdominal incision, the duodenum was ligated immediately below the pylorus and the drug solution was injected into the duodenal tract at a position 2 cm below the pylorus. The abdomen was closed and the blood sample was drawn at designated times. In studies with bile deprived rats, the common bile duct was ligated 5 mm from the opening to the duodenum, the abdomen was closed and then the rat was fasted for 18 h before drug administration.

In situ absorption studies

The recirculation experiment with the rat small intestine was carried out according to Kakemi's method (Koizumi et al., 1964). The initial concentration of SL-512 in the perfusion fluid was 0.01 μM. Perfusion media were pH 6.0 phosphate buffer, MCT and MBLA. The volume of the perfusion fluid was 50 ml with a flow rate of 5 ml/min. Sample fluid (0.5 ml) was drawn from the medium reservoir at 15, 30, 45 and 60 min after initiation of the experiment. The apparent absorption rate constant k was calculated by the equation

$$k = -2.303\,(V/t)\log(C/Co)$$

where V is the initial volume of the perfusion fluid, Co the initial drug concentration, and C the drug concentration at time t.

RESULTS AND DISCUSSION

Characteristics of model lipids and SL-512

MCT and MBLA were selected as models for vehicle lipids. MCT is known to have a much higher digestibility than long chain triglyceride (Greenberger et al., 1966). For instance, it has been reported that when 50 mg of trioctanoin was injected into the rat duodenum, 58% of it was absorbed within 10 min (Playoust and Isselbacher, 1964). The clinical usefulness of MCT has been discussed elsewhere (Greenberger and Skillman, 1969; Senio, 1969). Due to its high digestibility, MCT has recently been used as a nutrient for patients with malabsorption (Holt et al., 1969) or hyperlipemia (Furman et al., 1965). Moreoever, a relative ineffectiveness of MCT in slowing gastric emptying has been suggested (Hunt and Knox, 1968).

On the contrary, MBLA was selected as a typical model for poorly digestible lipids. It is a synthetic lipid which has the ability to retard cholesterol absorption (Fukushima et al., 1968, 1969). It is considered that resistance to enzymatic metabolism in the intestinal tract is the cause of poor digestion and absorption of this lipid (Nagata et al., 1971). With oral administration of this lipid to rats, 60% of the administered dose of 4–100 mg/rat of MBLA was recovered unabsorbed in 24-h feces (Fukushima, 1969).

In order to assess the affinity of the model drug SL-512 to MCT and MBLA, the

apparent partition coefficients of the drug between pH 6.0 phosphate buffer and these two lipids were determined. SL-512 showed an extremely satisfactory distribution to both lipids, while the partition coefficient for MBLA was slightly higher than that for MCT.

The in vitro transfer rate between the lipid and aqueous phases was also determined. The rate from aqueous phase to lipid phase was each 700 and 1800 times larger than that from lipid phase to aqueous phase for MCT and MBLA, respectively. These data are summarized in Table 1.

Serum level of SL-512 after oral or intraduodenal administration to rats

In view of the fact that MCT is a digestible lipid while MBLA is a poorly digestible lipid, it would be reasonable to assume that the absorption of SL-512 which has strong affinity to those lipids (Table 1) would be affected by that of the lipids. Therefore, the drug would be absorbed without any difficulty when MCT is administered and with some difficulty when MBLA is administered. Solution of SL-512 in MCT and MBLA were administered orally to rats. Fig. 1 shows the time course of serum levels of SL-512 for these two preparations. As expected, the MBLA solution gave a low serum level, while MCT solution gave a high level, with a peak being about 4 times higher than the other. As mentioned in our previous paper, gastric absorption of SL-512 can be ignored in the present experimental conditions and thus the cause of these differences can be attributed to the gastric emptying properties of the vehicle lipids or their digestibility in the intestine.

However, similar results were obtained when these preparations were administered directly into the rat duodenum as shown in Fig. 2. It was therefore concluded that the major cause of the difference observed in the oral administration experiments was the difference in the digestibility of MCT and MBLA. The sustained release effect of SL-512 from MBLA is noteworthy, an absorption continued over 12 h as shown in Fig. 1.

TABLE 1

DISTRIBUTION OF SL-512 BETWEEN LIPID PHASE AND WATER PHASE AT 37°C

Lipid	Partition coefficient (lipid/pH 6.0 buffer)	Transfer rate (min^{-1}) [a]	
		Lipid → water	Water → lipid
MCT	7.32×10^2 (7.11–7.53)	4.78×10^{-4} (4.58–4.95)	3.50×10^{-1}
MBLA	1.78×10^3 (1.69–1.83)	1.09×10^{-4} 1.02–1.14)	1.94×10^{-1}

[a] See text for details on determination methods.

Data are expressed as the mean of three experiments. The range of the experimental value was shown in the parentheses.

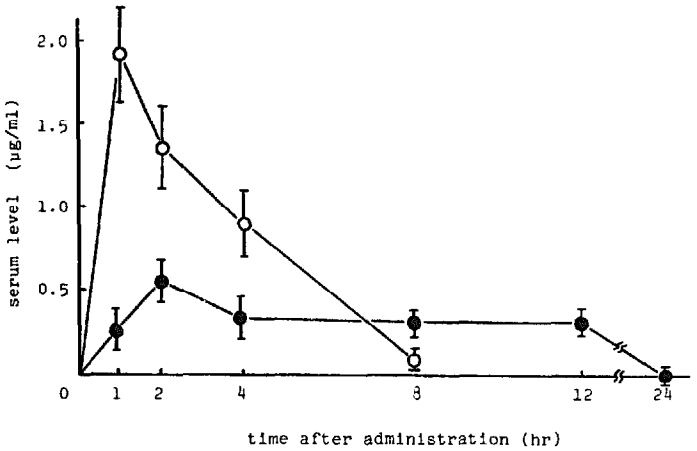

Fig. 1. Serum level of SL-512 after oral administration to rats. Dose level: SL-512, 2 mg/kg; MCT, 40 μl/rat; MBLA, 40 μl/rat. ○, MCT solution; ●, MBLA solution. Data are expressed as the means ± S.E. of at least 4 animals.

In situ recirculation experiment in the rat small intestine

In order to further examine the dependency of drug absorption rate on the digestion of vehicle lipids, in situ recirculation experiments were conducted. Lipid or aqueous solution was recirculated for 1 h in the rat small intestine and the apparent absorption rate constant was determined by measuring the disappearance of the drug from the perfusion fluid. The results are shown in Table 2. Although SL-512 was easily absorbed from the aqueous solution, it was completely unabsorbed from lipid solutions under these conditions where digestion of lipids could be neglected. The volume of lipids perfused (50 ml/rat) was extremely large compared with those administered in the oral administration experiment (40 μl/rat). Thus the high affinity of the drug to these lipids shown in Table 1 was confirmed. These results were essentially identical to similar experiments using rats

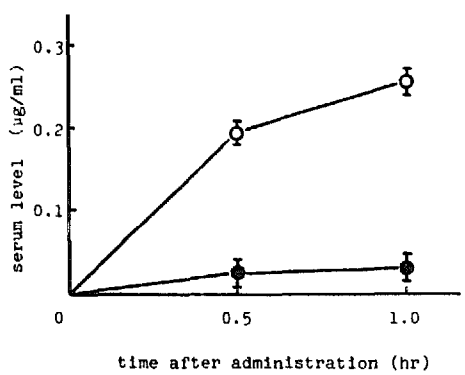

Fig. 2. Serum level of SL-512 after intraduodenal administration to rats. Dose level: SL-512 0.5 mg/kg in 40 μl/rat. ○, MCT solution; ●, MBLA solution. Data are expressed as the means ± S.E. of at least 4 animals.

TABLE 2

ABSORPTION RATE CONSTANTS OF SL-512 BY RECIRCULATION METHOD IN THE RAT SMALL INTESTINE

Data are expressed as the means ± S.E. of at least 5 animals.

Perfusion medium	Absorption rate constant (ml · min^{-1}) [a]
pH 6.0 buffer	3.78 ± 0.22
MCT	0.00 ± 0.00
MBLA	0.00 ± 0.00

[a] See text for details on determination method.

with ligated bile duct. In addition, when an aqueous solution of SL-512 was recirculated in the rat small intestine pretreated with these lipids, neither MCT nor MBLA changed the apparent absorption rate constant (data not shown).

Effect of lipid volume on the serum level of SL-512

The results shown in Table 2 also suggest that the effect of dose volume of the vehicle lipid is important, not only from the standpoint of gastric emptying as presented in our previous report but also from the standpoint of digestion of the lipid. In Fig. 3 the serum level of SL-512 at 1 h after intraduodenal administration of MCT solution was plotted against dose volume of the lipid over the range of 10 to 4000 μl/rat. At less than 100 μl/rat the effect of dose volume appeared more distinctly on the serum level in this experiment than on the gastric emptying rate presented in our previous report. It was therefore considered that in this range of small dose volume (10–100 μl/rat) the decrease

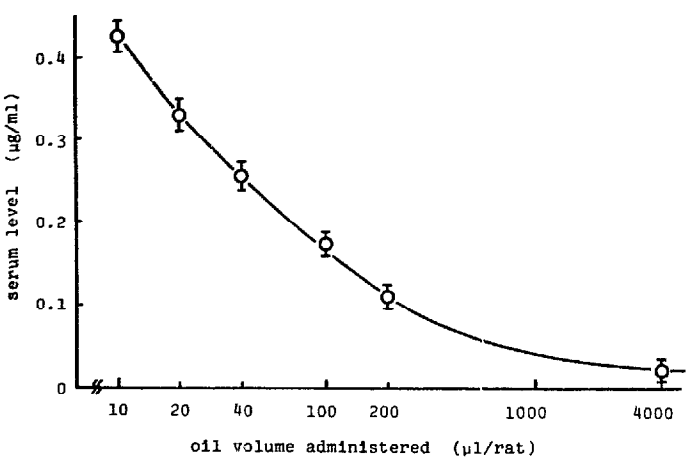

Fig. 3. Effect of administered lipid volume on the serum level of SL-512 at 1 h after intraduodenal administration of its MCT preparations to rats. Dose level: SL-512 0.5 mg/kg. Data are expressed as the means ± S.E. of at least 3 animals.

of SL-512 absorption associated with an increase of dose volume was mainly attributable to a decrease in the rate of digestion of the lipid after it is emptied from the stomach. This confirmed the significance of high affinity of the drug to the lipid vehicle.

On the other hand, above 200 μl/rat various factors, such as depression of the gastric emptying rate or the intestinal motility and a decrease in digestion rate of the lipid, may be involved in the decrease of the absorption rate of the drug.

Effect of bile duct ligation on the absorption of SL-512

As mentioned earlier, the benefit of reducing the dose volume of the lipid vehicle was clarified not only from the gastric emptying rate but also from digestibility following movement to the small intestine. In order to further investigate the role of lipid digestion, serum levels of SL-512 at 0.5 h after intraduodenal administration of corn oil, MCT and MBLA preparations were compared, using both intact rats and those with a ligated bile duct. The results are shown in Table 3.

While the serum level of SL-512 was in order the MBLA < corn oil < MCT in intact rats, it was strongly depressed for MCT and corn oil preparations in rats with ligated bile duct and the levels were almost the same among the three. In the rat, pancreatic juice as well as bile are introduced to the duodenum through the common bile duct. Thus, ligation of the bile duct may reduce intestinal lipid digestion through both dispersion and hydrolysis. A similar experiment was performed to investigate the contribution of dispersibility on intestinal lipid digestion using 20% w/v lecithin added to corn oil and MCT and 5% w/v polysorbate 80 added to MBLA, preparations that might be more dispersible.

This experiment could not demonstrate any increased absorption of SL-512 due to lecithin or polysorbate 80 in rats with ligated bile ducts (the level of significance of the *t*-test was $P > 0.1$ in all cases). This suggested that dispersibility of lipids is not a major factor affecting intestinal drug absorption from lipid preparations (Table 4). Moreover, in the case of MCT and corn oil preparations the serum levels of SL-512 were depressed in intact rats in which lecithin seemed to have inhibited absorption of lipids, probably

TABLE 3

EFFECT OF BILE DUCT LIGATION ON THE ABSORPTION RATE OF SL-512 FROM MCT, CORN OIL AND MBLA PREPARATIONS

Dose level: 0.5 mg/kg in 10 μl/rat. Data are expressed as the means ± S.E. of at least 4 animals. The levels of significance of the *t*-test between the data of intact and bile duct-ligated rats are shown in parentheses.

Vehicle	Serum level of Sl-512 at 0.5 h after intraduodenal administration (μg/ml)	
	Intact	Bile duct-ligated
corn oil	0.123 ± 0.008	0.024 ± 0.006 ($P < 0.05$)
MCT	0.204 ± 0.011	0.032 ± 0.007 ($P < 0.05$)
MBLA	0.032 ± 0.011	0.031 ± 0.005 ($P > 0.1$)

TABLE 4

EFFECT OF SURFACTANTS ON THE ABSORPTION RATE OF SL-512 FROM CORN OIL, MCT AND MBLA PREPARATIONS

Dose level: 0.5 mg/kg in 10 μl/rat. Data are expressed as the means ± S.E. of at least 4 animals. The levels of significance of the *t*-test between the data of intact and bile duct-ligated rats are shown in parentheses.

Vehicle	Serum level of SL-512 at 0.5 h after intraduodenal administration (μg/ml)	
	Intact	Bile duct-ligated
corn oil [a]	0.036 ± 0.011	0.017 ± 0.04 ($0.05 < P < 0.1$)
MCT [a]	0.126 ± 0.033	0.042 ± 0.009 ($P < 0.05$)
MBLA [b]	0.026 ± 0.006	0.026 ± 0.005 ($P > 0.1$)

[a] Vehicle lipids contained 20% w/v of soybean lecithin.
[b] Vehicle lipids contained 5% w/v of polysorbate 80.

due to the formation of larger micelles (Rodgers and O'Connor, 1975). In the case of the MBLA preparation neither ligation of the bile duct nor addition of polysorbate 80 altered the intestinal absorption of SL-512. These results corroborated the poor digestibility of MBLA. It was therefore suggested that, even at the small dose level employed in this study (less than 40 μl/rat), the decrease of the amount of lipids in the gut by digestion, probably by hydrolysis, was important for the absorption of the drug in lipids.

Thus under experimental conditions in which lipid digestion was depressed, the absorption rate of SL-512 was also lowered and the dependency of the drug absorption rate on that of the lipid vehicle, or in other words the importance of digestibility of the lipid vehicle, was confirmed.

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